Hypothesis: exposure to solvents may cause fibrosing alveolitis

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ABSTRACT: The incidence of fibrosing alveolitis, which can be caused by many agents, is increasing. In a proportion of patients, the aetiology is unknown (cryptogenic fibrosing alveolitis), but it has been suggested that environmental factors may play an important, but unrecognized, role in its pathogenesis. A review of the literature suggests that there may be a link between exposure to solvents, widespread occupational pollutants, and fibrosing alveolitis.

Experimental work in animals has shown that exposure to a wide number of solvents has been associated with the development of systemic sclerosis. Pulmonary involvement in systemic sclerosis is morphologically indistinguishable from fibrosing alveolitis, and a close relationship between the two diseases seems to exist. This close relationship and the experimental work linking solvent exposure to fibrosing alveolitis suggest that solvent exposure may be one cause of cryptogenic fibrosing alveolitis.

Determination of any occupational exposure of patients with cryptogenic fibrosing alveolitis may help in the understanding and prevention of this disease. Eur Respir J., 1994, 7, 1172–1176.
with "lone" cryptogenic fibrosing alveolitis suggests that there is frequently an immunological disturbance, such as positive rheumatoid factor, raised immunoglobulin G or M (IgG or IgM), or a raised atrial natriuretic factor (ANF) similar to that found in those patients with fibrosing alveolitis due to systemic diseases. In a series of patients with cryptogenic fibrosing alveolitis investigated by TURNER-WARWICK [8], either positive ANF or rheumatoid factor was found in 58% of cases. LOMEO et al. [9] described 10 patients with systemic sclerosis who presented with lung disease in the absence of cutaneous involvement. Pulmonary disease as the presenting symptom of systemic sclerosis can be difficult to differentiate from cryptogenic fibrosing alveolitis due to systemic diseases and can often result in misdiagnosis. Their patient group differed from typical systemic sclerosis in that there was a preponderance of men. LOMEO et al. [9] believed this suggested that occupational exposure might play a role in the development of systemic sclerosis sine scleroderma.

Cryptogenic fibrosing alveolitis probably represents the end-stage of antecedent acute or subacute disease provoked by a variety of causes. There is frequently an immunological disturbance of some kind, but it is still unclear whether these changes are causal or merely a result of the primary disturbance. Because of the insidious onset of symptoms in many cases, the aetiology of cryptogenic fibrosing alveolitis may go undetected.

### Occupational exposure

The study by JOHNSTON and co-workers [4] into the rising rate of mortality from cryptogenic fibrosing alveolitis found that deaths were more common in men, in the elderly and in the central parts of England and Wales. They suggested that occupational exposure to some factor might account for the concentration of the disease in the industrialized areas. They considered that exposure to agents previously unrecognized as being fibrinogenic or occult, or low exposure to known agents, could be a possible aetiological factor. The authors suggested that one such factor might be exposure to dust [10]. To test this hypothesis, they identified patients in the Nottingham (UK) area with cryptogenic fibrosing alveolitis and obtained up to four controls, matched for age and sex, drawn from the patient's own general practitioner's list. A self-administered questionnaire was sent to all subjects. The questionnaire included questions on previous areas of residence, past and present occupation and their duration, the duration of exposure to occupational dusts and their type, exposure to animals at work or at home, types of heating in previous and current housing, smoking history, and symptoms of allergy. Forty patients and 106 controls completed the questionnaire. The authors found that exposure to metal dust was significantly increased in the patients. A strong but nonsignificant association between cryptogenic fibrosing alveolitis and exposure to wood dust, and a more general association with occupations classified as dirty were also found. The patients were also more likely to have worked with cattle or to have been exposed to wood fires at home. These results, therefore, support the hypothesis that environmental factors have a role in the aetiology of cryptogenic fibrosing alveolitis.

### Exposure to solvents

Solvents are widespread environmental pollutants, found in a wide variety of situations from the home and office (being constituents of household and office products) to industry [11]. A large number of solvents are volatile and may, therefore, be frequently inhaled. In view of the widespread use of solvents and the association of cryptogenic fibrosing alveolitis with environmental factors, the possibility of a link between solvent exposure and cryptogenic fibrosing alveolitis should be considered. A review of the literature suggests that there may, indeed, be a link between exposure to solvents and fibrosing alveolitis.
Biochemical and morphological changes

Scadding [3] described acute fibrosing alveolitis as consisting of congestion and oedema of the alveolar walls and accumulation of inflammatory cells and fluid in the lower respiratory tract. Crystal et al. [12] described the early stages of fibrosing alveolitis as typically consisting of only minor derangements of the alveolar structure, with distortion of the alveolar walls due to accumulation of large numbers of neutrophils and macrophages mixed with small numbers of eosinophils and lymphocytes. As the disease progresses, Crystal et al. [12] noted marked changes in all components of the alveolar wall. These included the loss of type I and capillary endothelial cells, proliferation of type II cells and interstitial fibroblasts, and accumulation of type I collagen. In some cases, there is also limited destruction of the alveolar walls. Experimental work has demonstrated that exposure to solvents produces biochemical and morphological changes similar to those occurring in fibrosing alveolitis.

Acute exposure to solvents

Light and electron microscopy studies of the lung after inhalation, oral administration, or intraperitoneal injection of a number of different solvents have been reported [13, 14]. Electron microscopy showed that ultrastructurally there is damage to all components of the alveolar wall, with conspicuous changes in the granular pneumocytes (type II), necrosis of both types of pneumocyte, septal oedema and endothelial cell alterations [13]. Stewart et al. [14] described the effects of an intratracheal injection of 3-methylcholanthrene, and also the effects of inhalation of carbon tetrachloride, trichlorethylene or gasoline vapour on rat lungs. Ultrastructural examination revealed that, as with fibrosing alveolitis, cytoplasmic changes included loss of type I pneumocytes followed by irregular proliferation of type II pneumocytes. Transformation of the hypertrophied type II pneumocyte was evident, with relatively few surfactant lamellae apparent. All procedures produced a marked and reproducible reduction in secretion of pulmonary surfactant, as determined by bronchoalveolar lavage (BAL).

Chronic exposure to solvents

The effect on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane and 1,1-dichloroethylene has been investigated [15]. In all species of animals exposed to the solvents, histopathological examination of the lungs revealed nonspecific inflammatory changes. In some cases, there was evidence of interstitial inflammation and pneumonitis and varying degrees of lung congestion. Although the authors did not attribute the inflammatory condition to solvent exposure, such changes were only found occasionally in the control animals. This suggests that solvent exposure led to the inflammatory changes.

Lykke et al. [16] studied rats exposed to an atmosphere contaminated with petrol vapour, at a concentration of 100 parts per million (ppm) for up to 12 weeks. There was variability of time of onset of changes. Nevertheless, there were three groupings of pathological changes which represented an overall pattern. The earliest change consisted of a thickening of the interstitial plane. In the following weeks, there was an enlargement of type II pneumocytes, followed by degeneration of surfactant organelles of the hypertrophied type II pneumocytes, which correlated with the appearance of focal alveolar collapse and associated interstitial fibrosis. During weeks 9–12 of exposure, irregular foci of fibrosis were found with increasing frequency and were associated with alveolar distortion and collapse. Lykke et al. [16] suggested that their experimental technique, because of the rapidity with which lesions are introduced in the rat lung, provided an economic and reproducible model for the study of pulmonary fibrosis, which might well lead to a better understanding of fibrosing alveolitis.

Chronic exposure to diesel exhaust (a mixture of diesel hydrocarbons and volatile aldehydes, and gases such as NOx, SOx and CO) has also been found to produce fibrosis [17–19]. In cats, light and electron microscopy showed changes similar to that of fibrosing alveolitis, with type II pneumocyte hyperplasia and alveolar macrophages sequestered in interstitial and alveolar spaces [17]. Hyde et al [18] concluded that chronic exposure to diesel fumes has a persistent fibrogenic effect on the lung. Also, in rats, Mauderly et al. [19] found that exposure to high levels of diesel exhaust produced a progressive fibrotic lung disease.

Solvents, cryptogenic fibrosing alveolitis and systemic sclerosis

Systemic sclerosis is a multisystem disease, characterized by widespread fibrotic and degenerative changes in the skin, vasculature and internal organs [20]. Pulmonary involvement in systemic sclerosis produces changes in the lung that are morphologically indistinguishable from cryptogenic fibrosing alveolitis [9, 21]. As in fibrosing alveolitis, the aetiology of systemic sclerosis is unknown, but dysfunction of the immune system is important to the pathogenesis of the disease. Again, like fibrosing alveolitis, a number of agents have been implicated as potential causes of systemic sclerosis. An overlap between the two diseases is seen with bleomycin which, in two patients, has been reported to produce cutaneous fibrosis indistinguishable from that encountered in systemic sclerosis [22], and also produces progressive pulmonary fibrosis in up to 5–10% of patients [7].

Occupational exposure to solvents has already been associated with the development of systemic sclerosis [23–28]. In systemic sclerosis, a number of aromatic hydrocarbon solvents (toluene, benzene and xylene) and aromatic mixes (white spirit and dieselene) as well as chlorinated hydrocarbons (trichloroethylene and perchloroethylene) appear to be offending agents [24]. In a survey of 61 patients with systemic sclerosis, Czirjak and
SZEDEGI found no fewer than 19 female patients who had been exposed to chemicals [28].

Given the close relationship between fibrosing alveolitis and systemic sclerosis, and the experimental work linking solvent exposure to fibrosing alveolitis in animals, it seems very probable that some cases of cryptogenic fibrosing alveolitis may, in fact, be due to environmental exposure to solvents.

There have been a number of clinical reports following acute exposure to solvents. WANG and IRONS [29] reported the case of a 25 year old aircraft mechanic exposed to high levels of gasoline vapour in an unpurged wing tank. Autopsy revealed acute pulmonary oedema. POKLIS and BURKETT [30], in a review on gasoline sniffing, report that gasoline intoxication commonly leads to pulmonary oedema even in delayed deaths. NIERENBERG et al. [31] describe the case of a 42 year old woman exposed to concentrated vapours from mineral spirits. On the day of exposure, the patient complained of increasing dyspnoea at rest and vague chest discomfort. The patient then slowly developed profound hypoxia and apparently noncardiogenic pulmonary oedema. Since detailed studied of these patients were not reported, it is not possible to say whether these were cases of acute fibrosing alveolitis or, perhaps more likely, cases of acute respiratory distress syndrome (ARDS).

However, a recent report of deaths from interstitial lung fibrosis of workers in a Spanish textile factory [32] highlights the need to be aware of the possible link of exposure to solvents with development of cryptogenic fibrosing alveolitis. Five women workers, all employed as aerosol paint sprayers in a textile plant, died of what was described as "lung interstitial fibrosis related to occupational exposure to chemicals". Their workplace contained no exhaust ventilation, no protective screen, and only two protective masks among 17 workers. Regular nose-bleeding and mucous drying had affected the women who died and also other workers in the factory. The symptoms steadily worsened, with breathing problems developing later. The spray paint contained a number of chemicals (table 1) including 1,1-dichloroethylene and 1,1,1-trichloroethane, which in the animal experiments of PRENDERGAST et al. [15] were shown to produce inflammatory changes. In addition another ingredient, white spirit, has been associated with systemic sclerosis [21].

Investigations by the Spanish Labour Inspectorate and the Local Health Authority of this factory and 14 others performing similar work, have so far confirmed 69 cases of workers with diffuse lung fibrosis. The American National Institute of Occupational Safety and Health (NIOSH) is currently investigating these cases, to determine which particular agent was responsible for the development of the fibrosis.

Conclusions

Every effort should be made to determine any occupational exposure of patients with cryptogenic fibrosing alveolitis in order to try to understand, and so to prevent, this disease. Experimental and clinical evidence suggest that exposure to solvents is a probable cause of fibrosing alveolitis. When an initiating agent for cryptogenic fibrosing alveolitis is identified, it will then be possible to carry out further important investigations, such as bronchoalveolar lavage, which may develop a greater understanding of the processes which link alveolitis to the formation of fibrosis.

References


<table>
<thead>
<tr>
<th>Table 1. – Chemicals used in textile factory</th>
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<tr>
<td>Acracfix FHN (Contains 1-chloro-2,3-epoxipropanol, 2,3-dichloro-2-propanol)</td>
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<tr>
<td>Acromol W Pasta (Acrylin resin in aqueous dispersion with 1,1-dichloroethane)</td>
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<td>Acramin FWN (Polyamidamines)</td>
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<tr>
<td>Emulsionate L (Contains polyglycol esters and ethylene oxide)</td>
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<td>White spirit</td>
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<td>Solvethane (1,1,1-trichloroethane, dichloromethane, butyl alcohol)</td>
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<td>Disolvente 1-52 (petroleum solvents)</td>
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<td>Acetic acid</td>
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